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09/228,639	01/12/1999	SUSAN LOUISE WESTON	07164.0008	8318

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/228,639	Applicant(s) WESTON ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 14-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *26* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 12, 2002. Currently, claims 1-3, 5, 14-18 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's amendments to the claims, arguments or declaration.

3. This action is FINAL.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Newly Amended Claims 1-3, 5, 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (EPO 497527A1, August 5, 1992) and Ferrie et al (Am. J. Human Genetic, Vol. 51, pg. 251-262, 1992) in view of Newton (Nucleic Acids Research, Vol. 17, pages 2503-2516, 1989) in view of Estivill et al (Human Mutation, Vol. 10, pg. 135-154, 1997) and CFGAC (Cystic Fibrosis Genetic Analysis Consortium, Human Mutation, Vol 4, pg. 167-177, 1994)

This rejection is directed to the claims which require primers comprising specific SEQ ID NO:s.

Little et al. (herein referred to as Little) teaches a method for detecting single nucleotide variations in the cystic fibrosis gene by amplification refractory mutation system (ARMS). The ARMS method includes treating the sample with nucleoside triphosphates, an agent for polymerization and a diagnostic primer. Moreover, Little teaches that ARMS is able to selectively amplify multiple sites to obtain multiple amplification products to be distinguished simply, accurately, and with minimal operator skill thus providing a robust technique for screening a single sample for multiple nucleotide variations (pg. 2, lines 47-50). Little teaches numerous primers for ARMS analysis of the cystic fibrosis gene (pg. 27-29). Primers for 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H mutations are provided. The instant primers of SEQ ID NO: 12, 16, 17, 18 are identical to the Little primers 1879, 1880, 1879, 2072, respectively. Little teaches an ARMS reaction in which G542X, F508(M), 621+1 G>A, G551D mutations are multiplexed and analyzed. Little teaches placing the primers and reagents for the method in a kit.

Ferrie et al. (herein referred to as Ferrie) teaches the development of a multiplex ARMS test for common mutations in the CFTR gene. Ferrie teaches that ARMS systems have numerous advantages over other PCR-based systems including rapid, reliable, nonisotopic, and easily obtained results (pg. 251-252). Ferrie teaches that in principle, ARMS tests can be developed for any mutation. Ferrie teaches that ARMS tests have been developed for the following CFTR mutations: 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H. Moreover, Ferrie teaches how to increase sensitivity and design an ARMS system which would

provide the ordinary artisan with the tools needed to optimize a reaction for a specific need. Ferrie teaches altering the primer sequence has a large effect on the yield and specificity of an individuals reaction within the multiplex, while small changes were obtained by altering the primer concentrations (pg. 258, col. 1). Further, Ferrie teaches that the yield of the primer pair was affected by the rate of hybridization of ARMS primer to the target DNA and the rate at which the bases at the 3' end of the AMRS primer form a suitable substrate for Taq DNA polymerases (pg. 259, col. 2). Modification of the 3' sequence can change the specificity without significantly altering the calculated melting temperature (pg. 259, col. 2). Specificity may also be obtained by additional stabilization in which the choice of mismatched based was determined experimentally, given that purine/purine mismatches or pyrimidine/pyrimidine mismatches showed greater destabilization (pg. 259, col. 2). Also, specificity may be obtained by reducing the primer concentration and inclusion of control PCR reactions (pg. 259, col. 2). Ferrie also cites other references which discuss improving specificity by reducing the concentration of dNTP in the reaction (pg. 259, col. 2). Long primers (30 mers) ensured false priming events were minimized and that primer template interactions were stabilized and minimizing the disruptive effect of DNA polymorphisms (pg. 260, col. 1). Yields of the reaction needed to be relatively similar. Finally, ARMS multiplex has proved extremely reliable and has made the greatest impact on the speed of delivery of results (pg. 260, col. 2).

Newton teaches analyzing mutations in DNA using the amplification refractory mutation system (ARMS). Newton teaches the system is simple, reliable, and non-

isotopic and will distinguish between alleles (abstract). Newton teaches how to design the allele specific primers immediately adjacent to the mutation and even teaches that additional deliberate mismatches near the 3' end are appropriate. Newton teaches control primers to the apolipoprotein B gene.

Estivill et al. (herein referred to as Estivill) teaches geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. There mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. G542X, W1282X, N1303K, F508(M), G551D are taught to be the most common mutations. Furthermore, all of 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations are common in more than one region (Table 2 and 3).

Furthermore, CGFAC teaches that 24 of the most common mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. The specific frequencies in which these mutations are found are provided.

Neither Little, Ferrie, Newton, Estivill, nor CGFAC specifically teach SEQ ID NO: 5, 7, 8, 10, 14.

Therefore, it would have been **prima facie** obvious, given all of the teachings in the art, to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Little, Ferrie and Newton in view of Estivill and CGFAC to obtain the claimed method as a whole. Little teaches primers for ARMS reactions to

determine mutations in the CTFR gene. Ferrie teaches the modifications needed to be made to perform ARMS multiplex analysis. Little teaches numerous primers for ARMS reactions to determine mutations in the CTFR gene, for each of the claimed mutations except 3849+10kb C>T, R1162 and R334. The ordinary artisan would have been able to have performed routine experimentation to optimize the ARMS systems desired for the particular situation. All of the claimed mutations were known at the time the invention were made, as exemplified by Estivill and CFGAC. With respect to primers for these mutation, designing ARMS primers to these known primers would have been obvious to the ordinary artisan, as taught by Newton. Further Estivill and CFGAC taught the relative frequencies of the mutations in numerous populations. Thus, the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC.

The ordinary artisan would have been motivated to determine whether the mutation was present in a sample using the multiplex ARMS method of Ferrie since the ARMS method is rapid, reliable and nonisotopic. The ordinary artisan would have further been motivated to have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of Ferrie. Optimizing conditions for the multiplex reaction are taught by Ferrie. Therefore, the ordinary artisan would have been able to optimize the teachings in the art to generate a method which analyzes the 12

mutations claimed. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive.

The ordinary artisan would have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of optimization by Ferrie. Further, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the primers taught by Little, Ferrie and Newton in view of the known CFTR gene, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited reference in the absence of secondary considerations. The instant primers are designed to be ARMS primers (or allele specific primers). As taught by Netwon these primers have distinct characteristics which require the primers to be immediately adjacent to the mutation. Thus, since the known primers have a specific location within the known CFTR gene, designing of

ARMS primers would be directed to a specific location of the gene, rather than anywhere on the gene.

With respect to Claim 16 and 18-19 directed to sets of primers and kits comprising control primers, Newton teaches control primers directed to apolipoprotein B gene which encompass the instant SEQ ID NO: 1 and overlap SEQ ID NO: 2. Therefore, modifying control primers to a known region would have been functionally equivalent primers. Claim 16 and 17 with respect to SEQ ID NO: 1 are directed broadly to comprising primers, therefore, the Control 1 primer of Newton falls within the scope of the Claim.

With respect to Claim 17, the ordinary artisan would have been motivated to have placed the primers into a kit, as taught by Little. Reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged primers for ARMS multiplex analysis of CFTR in a kit for the expected benefits of convenience and cost-effectiveness of practioners in the art wishing to analyze the CFTR gene.

Since Estivill and CFGAC provides the frequencies of CFTR mutations, Ferrie teaches the ordinary artisan how to optimize multiplex ARMS reactions, and Little teaches ARMS reactions are appropriate for determining single mutations in the CFTR, it would have been obvious to have designed a multiplex reaction which suited the individual needs of the artisan as all such modification would have produced functional equivalent results based upon the teachings of Little and Ferrie. Therefore, the generic

multiplexing reaction of 12 well known mutations in a well known gene which causes cystic fibrosis would have been obvious.

Response to Arguments

The response traverses the rejection. The response asserts that the claims are not drawn to individual primers, but specific primer sets themselves. This argument has been reviewed but is not convincing because the rejection of record is directed to the specific combination of primers which are claimed. The response asserts that the particular sets of primers disclosed are unique and non-obvious and none of the references disclose the specific combination of primers taught. The examiner acknowledges that the specific combination of primers is not taught, however, the rejection is drawn to obviousness of the primer sets. The examiner has provided motivation to combine ARMS primers for the specified mutations into a multiplex analysis method. Selection of the twelve well known mutations in a well known gene which cause cystic fibrosis would have been obvious for the expected benefits of obtaining a large screen of the frequent mutations.

The response argues that the claimed set of primers is not merely an optimization of a known set of ARMS assay primers and conditions. This argument has been reviewed, but is not convincing because, conditions or parameters for multiplex analysis are well known. The target sequence has been taught by the art, the mutations have been taught by the art, the frequencies of the mutations have been taught by the art, how to design ARMS primers has been taught in the art, and optimization of multiplex reactions has been taught in the art. Therefore, each of the conditions and

parameters for the ARMS multiplex analysis of 12 mutations in the CFTR gene has been taught by the art. As provided by In re Aller, the general conditions of a claim have been disclosed. The prior art teaches that parameters which may be tweaked are discussed at length in Ferrie. Therefore, the general parameters are taught in the art to allow for the optimization of primers in a single system.

The response asserts that the disclosure of the template sequences does not render the design of such primers obvious. This argument has been reviewed but is not convincing because the structure of ARMS primers is very specific. Newton teaches that mismatch at the final base allows for the discrimination between the nucleotide sequences. Therefore, the specific sequences would have been functional equivalents to those sequences already taught in the art or would have been easily obtainable based upon the direction for designing ARMS primers of Newton.

The response appears to assert that the lengths of the primers are critical. However, the claims are directed to primers comprising the recited sequences. Therefore, the primers appear to allow for additional nucleotides on either the 3' or 5' end. However, the claims are directed to allele specific primers, therefore, it is unclear how the claim could allow for additional nucleotides on the 3' end and the functioning of the invention.

The response argues that the examiner has used an obvious to try standard which is impermissible. This argument has been thoroughly reviewed and found not persuasive because there is a nearly certain expectation of some success for designing ARMS primers based upon the teachings of Newton and multiplexing such primers.

While some primer sets containing certain primers and other optimal conditions may be preferred, there is a reasonable expectation of success rather than obviousness to try.

The response further maintains that the claimed sets of primers unexpectedly work together in the multiplex ARMS reaction to detect the presence or absence of twelve known CFTR mutations. The response supports such statements with a Declaration showing the unexpected results. Moreover, as provided in MPEP 716.02 (d), unexpected results must be in commensurate scope with the claims. "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)." The declaration filed September 12, 2002, teaches that lengths of primers was varied and that some results were "weak, very weak, nonspecific- i.e. unacceptable (page 5 of declaration). As provided by the declaration, on page 9 of the faxed document, the final tube B was altered in that 621+1/R117HC was added 3 bases longer at the 5' end. The declaration states that "primer 621+1/R117HC was changed when it failed to work as expected in the final stages of prototype testing" (point 7 of declaration). It is presumed that such tweaking was performed to obtain the optimal results of the claimed invention. Thus the declaration appears to indicate that the length of the primers is significant and that the optimal

unexpected results are dependent upon length. Therefore, the claims would not been commensurate in scope with the unexpected results.

Moreover, sequence information regarding Tube A has not been provided for analysis. Therefore, the unexpected results of the claims also appear to be limited to Tube B. Thus, claims directed to only primers in Tube A, namely Claims 3, 14, 17-19 do not appear to be commensurate in scope with the unexpected results.

As discussed on November 22, 2002, in an interview with William Schmidt, claims limited to the unexpected results of the declaration would be considered allowable. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

5. No claims allowable over the art.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
November 27, 2002

W. Gary Jones
Supervisory Patent Examiner
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